Medical Therapy of IBD in 2009

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Medical therapy for Inflammatory Bowel Disease (IBD) has advanced dramatically in the last decade with the introduction of targeted biologic therapies, optimization of older therapies including immunomodulators and 5-Aminosalicylic acid (5-ASA) drugs, and a better understanding of the mucosal immune system and genetics involved in the pathogenesis of IBD. Here we update the medical management of IBD in 2009.

The goal of IBD therapy is to induce, and then maintain, remission. Since we are unable to predict disease course at diagnosis, the current paradigm of treatment is a step-up approach: moving to aggressive, powerful therapies only when milder therapies with less potential side effects fail or when patients declare themselves to have aggressive disease. If our ability to stratify risk at diagnosis improves, we may see a paradigm shift to top-down therapy with the powerful drugs used first line to change the course of the disease and improve outcomes.[1]

5-ASA

Sulfasalazine and 5-aminosalicylic acid formulations are mainstays of treatment for mild to moderately active ulcerative colitis and mild **Crohn's disease (CD)**.[2]

Ulcerative Colitis

Both topical and oral forms of the 5-ASA medications can be used depending on the distribution of colonic disease. For ulcerative proctitis (rectal involvement up to 20 cm), mesalamine suppositories are effective at inducing and maintaining remission.[3] In patients with left-sided ulcerative colitis (below the splenic flexure), mesalamine enemas can induce and maintain remission. UC extending beyond the splenic flexure, also know as extensive colitis, requires oral therapy. However, rectal mesalamine (either suppository or enema forms) can have an adjunctive role in treating patients with pancolitis, as diarrhea and tenesmus are often due to the left-sided disease. Combining oral and topical therapy leads to faster resolution of rectal bleeding and is also more effective at maintaining remission compared to oral therapy alone. Oral formulations of the drug are differentiated by several factors including the drug delivery system, pH dependence, azo-bonding, and even time-controlled release. All seem to work equally well for mild to moderate UC. Dosing can be adjusted based on the severity of disease. For mild disease, 2.4-3 grams per day is preferred, whereas higher doses (4- 4.8 grams per day) are needed to induce and maintain a remission in moderate UC. Severe disease requires more aggressive therapy (i.e. corticosteroids) to induce remission, and then 5-ASA drugs can be utilized to maintain remission. Finally, a meta-analysis suggested 5-ASA use in UC may decrease colorectal cancer risk by 50%.[4] Adherence to medical therapy is strongly associated with staying in remission compared to nonadherence (see graph below).[6] Cost, pill burden, side effects, inadequate understanding for the rationale for maintenance therapy are some of the factors associated with non-adherence.[6]

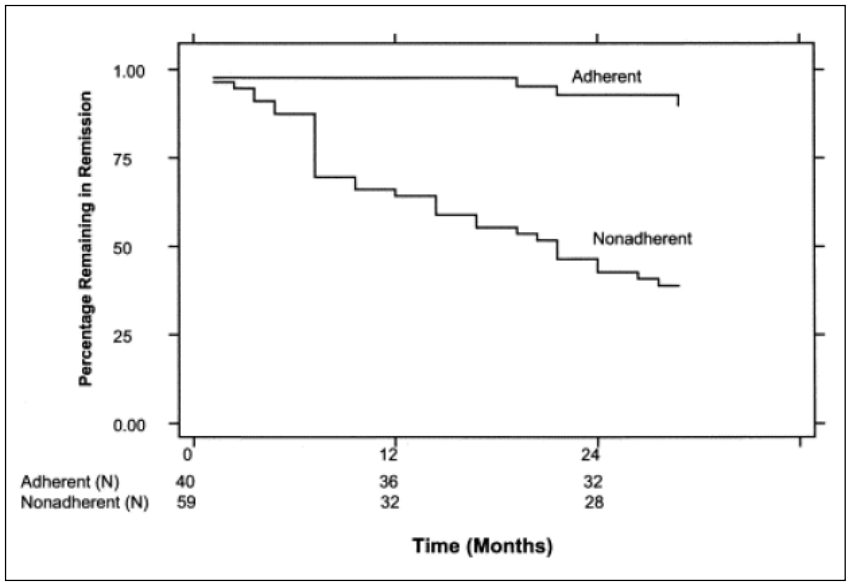
Crohn's Disease (CD)

Mesalamine has some benefit in inducing remission for patients with ileal or colonic CD. However, meta-analyses have shown 5-ASA is no better than placebo in maintaining medically induced remission.[5] Nevertheless, clinical experience favors use of mesalamine in mild CD because of its safety and perceived efficacy in practice. Mesalamine is not effective in patients with moderate or severe CD or in patients requiring steroids to induce remission. The time or pH dependent formulations are most useful for patients with small bowel involvement. 5-ASA drugs have a limited role in preventing/delaying post-operative recurrence.

Overall, 5-ASA drugs are generally tolerated well; but patients and primary care physicians should be aware of potential side effects. Up to 30% of patients taking 4 grams per day of sulfasalazine are intolerant. Side effects include bone marrow suppression, impairment of folic acid absorption, and rash. The newer 5-ASA formulations avoid sulfa related side effects of sulfasalazine. However, both sulfasalazine and 5-ASA formulation can have adverse effects including headache, pancreatitis, GI upset, hair loss, and rarely pulmonary fibrosis, paradoxical worsening of colitis and renal toxicity. The 5-ASA drugs are ineffective in severe disease requiring hospitalization. All patients on 5-ASA therapy should have a baseline creatinine checked prior to starting therapy, several months into therapy, and then annually. Patients with a severe aspirin allergy should not be prescribed 5-ASA.

Antibiotics and Probiotics

Because of the postulated role of bacterial flora in the pathogenesis of IBD, there is great interest in both antibiotics and probiotics. Efficacy of probiotics has not yet been shown in high quality trials;



therefore data do not support use of any probiotic in CD or UC.

Limited data support a role for antibiotics in CD but not in UC except for hospitalized patients with fulminant colitis at risk for sepsis. After colectomy with ileoanal pouch, some patients will develop pouchitis which generally responds to antibiotics (Metronidazole, Ciprofloxacin, or both).

Antibiotics have some benefit in treating CD. Metronidazole is effective in treating mild to moderate CD. There is benefit in perianal disease as well as in delaying recurrence after segmental surgical resection.[7] Ciprofloxacin is also useful in treating CD (both luminal and perianal).

Antibiotic therapy in CD is limited by the side effect profile of the drugs. Metronidazole can lead to peripheral neuropathy and can cause a disulfiram-like reaction with concurrent alcohol use. Ciprofloxacin is contraindicated in children and can cause tendonopathy in all patients using the medication. Use of antibiotics is a risk factor for *Clostridium difficile* infection, an increasingly common problem for many patients, including those with IBD.

Steroids

Corticosteroids, used for over 50 years to treat IBD, are used to treat moderate to severe UC. Steroids have no role/efficacy in maintenance of remission. Steroid enemas have been beneficial in distal UC; systemic absorption can lead to steroid related side effects. For patients who do not tolerate 5-ASA enemas, cortenemas and particularly cortifoam may be better tolerated initially.

Corticosteroids in CD have been studied extensively. Two large trials validated their use for inducing remission (NCCDS and ECCDS).[8] However, concern exists over patient outcomes once they are started on a prolonged course of steroids. A Minnesota cohort of Crohn's patients [9] was followed after steroid treatment. Of those who responded, only 32% had a prolonged response to steroids (at one year), 28% had become steroid dependent, and 38% had undergone surgery. Increasingly, clinicians appreciate that the need for steroids in IBD defines a subgroup of patients with aggressive disease. In this subgroup, immunomodulator therapy or a biologic will likely be needed in CD and may be needed in UC to achieve steroid-free remission. Steroids are neither effective nor recommended as maintenance therapy or for post-operative prevention of recurrence.

Dosing of corticosteroids for IBD is different than that used for pulmonary and rheumatologic disorders. Prednisone can be given orally at a dose up to 60 mg per day with a slow taper over months. Higher doses have no additional benefit and are associated with worse side effects. Too rapid a taper can lead to relapse. Intravenous steroids are preferred for hospitalized patients who are generally sicker and may have impaired absorption.

Budesonide, a steroid with less systemic side effects than oral prednisone, is designed to release in the distal ileum / proximal colon and hence is ideal for inducing and prolonging remission in mild to moderate CD involving those areas. Budesonide has fewer side effects than prednisone, but still has the potential for adverse effects and can suppress the hypothalamic-pituitary axis.[10]

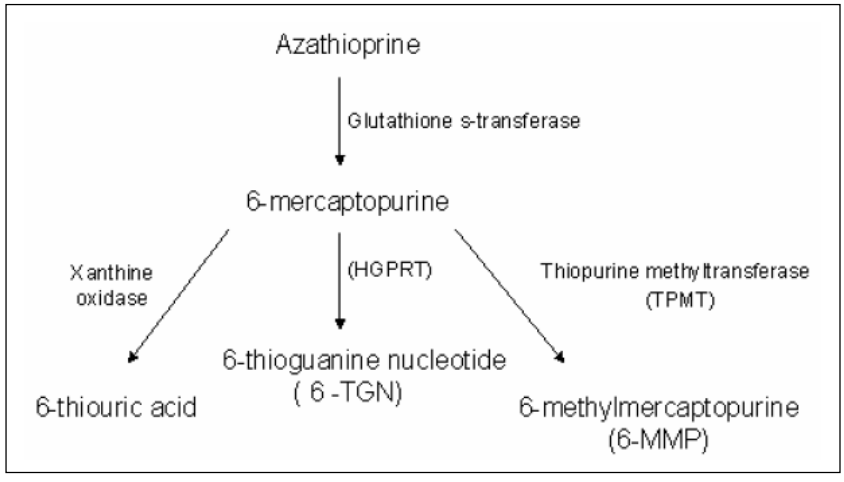
Numerous steroid side effects include acne, striae, "moon facies", edema, mood/sleep disturbance, as well as glucose intolerance. Prolonged use of steroids can lead to myopathy, osteoporosis, cataracts, and avascular necrosis of the femoral head. Another important concern for those on prolonged steroids is an increased susceptibility to infection. An analysis of the TREAT registry concluded that steroid and narcotic use were both independently associated with increased risk of infection and mortality in CD.[11] Finally, tapering steroids is not easy, as abrupt withdrawal can lead to acute adrenal insufficiency.

Immunomodulators

Immunomodulators, in particular **azathioprine (AZA)** and **6-mercaptopurine (6MP)**, have long been used for treatment of UC and CD. **Methotrexate (MTX)** also has immune-modifying and anti-inflammatory properties, leading to its use in rheumatoid arthritis, psoriasis, as well as CD (but not UC). Cyclosporine, a powerful immunosuppressant, has been used for severe IBD.

AZA (2-2.5mg/kg qd) and 6-MP (1-1.5 mg/kg qd) are used in UC patients who are steroid dependent or unresponsive to corticosteroid or mesalamine therapy. These oral medicines are effective long-term steroid-sparing agents for UC and are useful in maintaining remission. However, these drugs do not reach maximal effect until 2-4 months of administration. Therefore, these drugs are usually initiated in concert with another form of therapy until they have reach steady-state levels. Cyclosporine has been used in steroid-refractory severe colitis in a last attempt to prevent colectomy.[12] Cyclosporine, if effective, is used as a bridge to AZA or 6-MP long term therapy. Therefore, cyclosporine should not be considered if a patient has already failed or is unable to take AZA/6-MP because of intolerance or side effects.

Immunomodulators are also used in the treatment of CD. Present et al [13] established the efficacy of 6-MP with a 70% response rate in patients with steroid- refractory CD. The mean time of treatment required for response was 3.1 months. In addition to decreasing disease activity, 6-MP had other beneficial effects, including healing and closure of fistulas and maintenance of remission in



both CD and UC. Methotrexate is a second-line therapy used for steroid-dependent or refractory CD. Studies have shown efficacy at inducing and maintaining remission with the intramuscular administration at a 25mg per week dose and 15 mg/week dose respectively. Oral MTX does not work as well in CD.[7]

AZA/6-MP can cause pancreatitis as well as hepatotoxicity and pancytopenia. Both agents are metabolized by **thiopurine methyltransferase (TPMT).** Individuals who are heterozygous for TPMT need a reduced dosage of the medication in order to avoid excessive myelosuppression. The rare patient (1 in 300) who has absent TPMT activity (recessive for 2 mutant copies of TPMT) will develop profound myelosuppression if given AZA/6-MP; hence their use is contraindicated in this rare situation. Complete blood count and hepatic function panels should be monitored. A CBC should initially be checked weekly, then every 2-3 months, along with liver enzymes, once on a steady dose. Allopurinol will increase the serum levels of AZA/6-MP metabolites which could lead to significant myelosuppression. Also, AZA/6-MP decrease serum levels of warfarin.

MTX must be administered in conjunction with folic acid. A majority of the side effects are gastrointestinal, including nausea and vomiting. MTX also has potential hepatotoxic, myelosuppressive, and pulmonary side effects. A baseline chest x-ray prior to MTX and subsequent monitoring of CBC and LFTs is advised. Patients have had adverse reactions with concomitant use of NSAIDS and penicillin while using MTX.

Cyclosporine has a host of serious side effects including potentially fatal opportunistic infections. **Pneumocystis carnii pneumonia (PCP)** prophylaxis should be given if cyclosporine is started. Cyclosporine can also lead to renal impairment, hepatotoxicity and seizures. Given its significant toxicity, including a mortality rate of 1 in 200, we suggest only experienced centers/clinicians use this therapy.

Biologics

The biologic medications have efficacy in moderate to severe UC and CD.[14] These medications include infliximab, adalimumab, and certolizumab pegol which all inhibit TNF-alpha. Infliximab is a chimeric anti-TNF alpha monoclonal antibody given intravenously. Adalimumab is a recombinant human monoclonal antibody which is administered subcutaneously and can be self-injected. Certolizumab pegol is a humanized anti-TNF alpha antibody FAB fragment that has been pegylated and is administered subcutaneously. All three are approved for use in CD; currently, only infliximab is approved for use in UC.

Infliximab was tested in UC patients who were refractory or intolerant to steroids and/or Azathioprine/6-MP and 5-ASA.[15] These studies showed that Infliximab was superior to placebo in establishing and maintaining remission, mucosal healing, discontinuation of steroids, and avoiding colectomy.

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Extensive data exist for use of biologics in CD. Infliximab was studied in a group of patients with moderate to severe CD who were refractory to steroids, ASA, and/or immunomodulators.[16] Patients who responded to an initial infusion had a statistically significant achievement of remission compared to placebo. Infliximab was later tested in patients with fistulizing CD.[17] This placebo-controlled study illustrated that infliximab was successful in treating patients with active fistulas with greater evidence of healing than placebo.

Adalimumab is effective in clinical studies in inducing and maintaining remission in moderate to severe CD..[18,19] Placebo-controlled studies demonstrated that patients naive to anti-TNF therapy had significant improvements in initiating and maintaining remission. Patients on adalimumab also had more steroid discontinuation and healing of fistulae compared to placebo. Concomitant use of immunomodulator therapy did not cause significant improvements in these studies. Therefore, monotherapy with a biologic is considered the preferred strategy in patients who have previously been on immunomodulators. Both adalimumab and infliximab have shown increases in quality of life, fewer hospitalizations and surgeries with maintenance use. Therefore, although these medicines are expensive, they may result in overall savings.

Certolizumab, the newest anti-TNF drug approved for use in CD,[20] has not yet been studied in fistulizing CD or as a steroid sparring agent.

Without head-to-head trials comparing the anti-TNF agents, there is no basis to recommend one over another. If one compares the trials (realizing different patient populations, different definitions of response and time points of assessment), the initial efficacy for inducing remission and maintaining remission for the first 6 months appear similar. Further experience will determine if a particular anti-TNF has an efficacy, safety or cost advantage. For those patients who lose response or have side effects, an alternate anti-TNF agent can be tried with some, although reduced, efficacy compared to a patient naive to anti-TNF therapy.

Safety of Biologics

Adverse reactions range from infusion or injection site reactions,[21] minor upper respiratory tract infections to serious infections and malignancies. Reactivated TB and fungal infections (particularly histoplasmosis) are a significant concern and should be considered in any patient with fever, and other symptoms suggesting infection.[22]

Non-Hodgkin's lymphoma has been reported in patients taking anti-TNF medications; however, it is not clear whether these lymphomas are related to anti-TNF agents, other agents, or underlying disease. Studies have yielded conflicting results on lymphoma risk with anti-TNF therapy ranging from no increased risk to a 3 fold increase in relative risk.

Hepatosplenic T cell lymphoma (HSTLC) is a rare, fatal disease that has been described in 16 IBD patients[23] between 2002 and 2008 (age range 12-58, 15 males, 1 female) who were using combination therapy with an anti-TNF and either AZA or 6-MP. Therefore, the current recommendation is to avoid combining an immunomodulator with an anti-TNF in younger males and in patients who have previously failed immunomodulators. Anti-TNF medications should be avoided in

patients with severe heart failure, demyelinating disorders, and active HBV. All patients should be assessed for TB and HBV prior to initiating anti-TNF agents; furthermore, patients should be prompted to remind all caregivers that they are on a powerful drug that can increase the risk of dangerous opportunistic infections.

Top Down Therapy in CD

One recent study compared early aggressive treatment with infliximab plus azathioprine versus a traditional step up approach. Patients randomized to early aggressive treatment had faster time to remission, less steroid use and higher rates of complete mucosal healing.[24] Whether this approach improves long term outcome without the potential side effects of these aggressive therapies is still under investigation.

A new landmark study, **SONIC (Study Of Biologic and Immunomodulator Naïve Patients In Crohn's Disease)**, investigated CD patients who had not responded to 5-ASA, antibiotics, or steroids or were steroid dependent.[26] These patients were naive to immunomodulatory agents and biologics and had CD for a shorter time compared to patients enrolled in previous trials with anti-TNF agents. Patients were randomized to AZA, Infliximab, or combination AZA + Infliximab. Infliximab monotherapy was superior to AZA monotherapy at 6 months. However, combination therapy was superior to both monotherapy arms. This study is the first to show that combining therapy has increased efficacy in CD. Previous studies did not document benefit with combination therapy. The earlier studies enrolled patients who had failed immunomodulators whereas the SONIC trial enrolled patients who were naive to both immunomodulators and anti-TNF agents. Longer term follow-up of patient outcome in this study is eagerly awaited to help clinicians guide therapy and balance benefits versus risks.[26]

Natalizumab

Natalizumab is a recombinant humanized antibody that targets alpha-4 integrin and thereby prevents inflammatory cells from getting to the gut and central nervous system and is effective in both **multiple sclerosis (MS)** and CD. **Progressive multifocal leukoencephalopathy (PML)** has been reported in 6 patients. Therefore, its use in CD patients is restricted to those have failed other therapies including at least one anti-TNF drug. Other drugs blocking cell trafficking and other aspects of intestinal inflammation are in clinical trials.

Surgery

Surgery has an important role in treating IBD and sometimes is the preferred alternative. It should not be seen as a last resort but an important option to consider depending on the clinical situation and the patient's preference. For example, a patient with 20 years of CD and symptomatic short fibrotic stricture with proximal dilation will not respond to any medical therapy and is best served by a surgical approach. The indications and options for surgery in both CD and UC are discussed in separate articles in this issue.

A team approach with the patient, gastroenterologist, surgeon and primary care physician can optimize outcome.

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Discussion of off-label usage and any productsor services

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